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(54) Pharmaceutical, veterinary and cosmetic compositions and uses.

(57) Pharmaceutic, veterinary and cosmetic compositions used for treating the human or animal body consist essentially of hydroxyalkylphosphine compounds such as tetrakis (hydroxymethyl) phosphonium sulphate and a pharmaceutically, veterinarally or cosmetically acceptable diluent or carrier.

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Description

PHARMACEUTICAL, VETERINARY AND COSMETIC COMPOSITIONS AND USES

This invention relates to the pharmaceutical, veterinary and cosmetic use of hydroxyalkyl phosphines and their derivatives and especially to their use for topical application to humans and animals to cure, prevent or alleviate fungal, bacterial and other microbial infections of the skin, or to alleviate skin odour.

In our application E.P. 0139404 A1 we have described the use of certain hydroxyalkyl phosphines for water treatment and in our unpublished application GB 8527793 we have described horticultural and agricultural uses of hydroxyalkyl phosphines to control mosses lichens and plant pathogens. We have now discovered that hydroxyalkyl phosphines are effective against a wide range of fungal, bacterial, protozoal and other microbial infections of humans and animals.

Our invention provides the prophylactic, therapeutic and/or cosmetic use for treating the human or animal body of hydroaxyalkyl phosphine compounds of the formula $[HORPR'_n]_xX_y$ wherein R is an alkylene group having from 1 to 4, preferably 1, carbon atoms, and R' may be the same or different and is an alkyl group having from 1 to 4 carbon atoms or, preferably, an −ROH group, X is an anion such that the compound is at least sparingly soluble in water, x is the valency of X, n is 2 or 3 and y is 0 or 1 such that (n + y) is 2 or 4; or an at least sparingly water soluble condensate of any of the aforesaid compounds.

Preferably the hydroxyalkyl phosphine compound is tris (hydroxymethyl) phosphine or a precursor or most preferably a tetrakis (hydroxymethyl) phosphonium salt. Particularly preferred are tetrakis (hydroxymethyl) phosphonium chloride, sulphate, bromide and phosphate. However X may be any compatible anion such as nitrate, fluoride, a phosphonate such as acetodiphosphonate, aminotris(methylenephosphonate), ethylene-diamine tetrakis (methylenephosphonate) or diethylene triamine pentakis (methylene phosphonate), a condensed phosphate such as pyrophosphate, metaphosphate, tripolyphosphate or tetraphosphate, chlorate, chlorite, nitrite, sulphite, phosphite, hypophosphite, iodide, borate, metaborate, pyroborate, fluoborate or carbonate or an organic anion such as formate, acetate, benzoate, citrate, tartrate, lactate, propionate, butyrate, ethylene diamine tetracetate, paratoluene sulphonate, benzene sulphonate or a surfactant anion such as an alkyl benzene sulphonate, alkyl sulphate or alkyl ether sulphate.

The hydroxyalkyl phosphine compound may alternatively contain 2 or more phosphorus atoms, and preferably the phosphorus compound is water soluble to a concentration of at least 10 ppm. more preferably at least 20 ppm. most preferably at least 100 ppm e.g. at least 0.5 g/l at 25°C. Such phosphorus compounds contain at least 1 hydroxyalkyl group, usually per phosphorus atom, and preferably at least 2 hydroxyalkyl groups per phosphorus atom. Such hydroxyalkyl groups are preferably of formula ROH, where R is as defined above. The group or groups joining the phosphorus atoms together may be of formula -R-, -R-O-, -R-O-R- or -R-NH-R or -R-R″-R- where R is as defined above and R″ is the residue formed by removal of two hydrogen atoms, bonded to nitrogen, from a di or polyamide or di or poly amine, such as urea, dicyandiamide, thiourea or guanidine. Such compounds with 2 or more, e.g. 3, hydroxyalkyl groups per phosphorus atom may be made by self condensation of compounds with 3 or 4 hydroxyalkyl groups attached to one phosphorus atom, e g. of formula $[HOR\ P\ R'_nO_m]_yX_x$ or with a compound of the formula $R''H_2$ such as urea. Condensation may be performed by heating at 40-120°C.

The hydroxyalkyl phosphine compounds are highly effective against fungi such as Trichophyton rubrum, T. mentagrophytes T. interdigitale and Microsporum canis which cause Athletes Foot, and/or Ringworm infections of humans.

The compounds are also very effective against various Streptococci such as S. pyogenes, which is responsible for a variety of human and animal diseases including Impetigo, Erysipalus, Scarlet Fever, Rheumatic Fever and Tonsilitis and other throat infections in humans and Mastitis of cattle, and S. Faecalis which is responsible for urinary infections such as Cystitis.

Other bacteria against which the compounds are effective include Proteus species such as P. mirabilis, P. vulgaris which cause urinary infections and pneumonia, Klebsiella pneumoniae, which causes pneumonia, and womb infections of mares, salmonella typhimurium and S. Enteritides which cause food poisoning in humans and poultry, Shigella boydii which causes Bacillary Dysentery, Bacillus cereus which causes food poisoning and Legionella pneumophila which causes Legionaires Disease.

The compounds are also effective against Candida albicans and Candida tropicalis, which cause Thrush, Sporotrichum schenckii which cause abscesses in humans and horses, Aspergillus fumigatus which causes pulmonary disease and pathogenic protozoa such as Naegleria or Acanthamoeba which cause Amoebic Meningitis.

The invention according to a preferred embodiment provides a method for the treatment of the skin of humans or animals which comprises applying thereto a hydroxyalkyl phosphine compound, and especially tetrakis (hydroxymethyl) phosphonium salts to inhibit fungal, bacterial or other microbial infections thereof.

The preferred method is applicable, for example, to the treatment of fungal infections such as Athletes Foot or Tinea (ringworm) and bacterial infections such as Boils, Erysipalus or Impetigo or to reduce foot odour, or for the treatment of Mastitis in cattle.

The hydroxyalkyl phosphine compounds are especially useful in antiseptic/fungicidal creams ointments, pastes, collodions, lotions, liniments and powders for treatment of Athletes Foot, Ringworm, Boils, and other infections and inflamations of the skin, in foot sprays, and in veterinary dips and udder washes.

The compounds may also be used in mouth washes and gargles for treating such condition as gum boils, Streptococcal infections and Oral Thrush. They are useful in pessaries and other preparations for treatment of Cystitis, Vaginal Thrush and other urinary and vaginal infections.

They may also be useful in topical, parenteral or oral preparations, for treatment, prevention and/or control of a variety of human and animal infections such as Salmonella infections in poultry and humans, Legionaires Disease, various types of Pneumonia, Staphylococcal infections, Rheumatic Fever, Plague, Scarlet Fever, Tuberculosis, Leprosy, Anthrax, protozoal infections, such as Amoebic Meningitis, Amoebic Dysentry, Malaria and Trypanosomiasis, vermal infections such as Hookworm, Filariasis, Toxocariasis, Bilharzia, Ascariasis, Tapeworm and Liver Fluke, and systemic fungal infections such as histoplasmosis, blastomycosis, paracoccidiomycosis, coccidiomycosis, and actinomycosis.

According to a further embodiment, therefore, our invention provides a pharmaceutical or veterinary composition comprising a pharmaceutically active proportion of a hydroxyalkyl phosphine compound according to the aforesaid formula and most preferably a tetrakis (hydroxymethyl) phosphonium salt, and a pharmaceutically acceptable diluent, carrier or solvent therefore.

The composition may comprise an aqueous or organic solvent such as sterile water, saline solution, ethanol, isopropanol or glycerol, or mixtures thereof or a hydrocarbon, glyceride or other oil, preferably emulsified with water or an aqueous based solvent.

Particularly preferred are compositions adapted for topical application containing the hydroxyalkyl phosphine compound carried in a cream or ointment base or adsorbed on or absorbed in an inert particulate solid such as talc, kaolinite, bentonite, diatomaceous earth, zeolite or other absorbent aluminosilicate or calcium carbonate. Alternatively the compounds may be encapsulated or micro capsulated in a pharmaceutically acceptable encapsulant such as sugar, fat, gelatin, resin or gum, such as gum acacia, gum arabic, gum tragacanth or a slowly soluble synthetic polymer, such as polyvinylalcohol or absorbed in a low release glass such as a phosphate glass.

Alternatively the compounds or solutions thereof may respectively be dissolved in or emulsified with liquified gaseous solvents in pressurised containers. The invention also provides medicated shampoos and medicated soap in bar, liquid crystal or liquid form containing the hydroxyalkyl phosphine compounds.

The compounds may be tabletted with suitable solids such as chalk, kaolin, sugar or salt or dissolved in syrups, linctus or saline drips.

The compositions may additionally contain other fungicides, bactericides or synergists, antiperspirants, lanolin or other skin softening or moisturising preparations, analgesics, antibiotics, emulsifiers, dispersants, carboxymethyl cellulose, soaps, surfactants, polymeric thickening agents, wetting agents, foam controlling agents, perfumes, flavourings, colouring, deodorants, reodorants and antiseptics.

A typical ointment, for instance, may contain soft parafin, petroleum jelly, emulsifying wax, and/or wool fat, optionally in admixture with liquid parafin and/or hard parafin, a cream may typically comprise an aqueous based emulsion of emulsifying wax, together optionally with soft parafin or other hydrocarbons, and/or wool fat. Creams may optionally contain buffers, such as citric acid/sodium phosphate. Ointments or creams may be combined with e.g. zinc oxide or calamine to form pastes.

The effective dose depends upon the nature and site of the infection. Typically the hydroxyalkylphosphine compounds exhibit bacterial and fungicidal activity at concentrations within the range 1 to 2000 ppm, especially 5 to 1000, preferably 10 to 500 e.g. 15 to 200 ppm. It is preferred to administer doses adapted to provide such concentrations at the site of infection, subject to toxicological constraints.

Compositions according to the invention typically contain from 0.2 to 20% by weight of the hydroxyalkylphosphine compound preferably 0.5 to 10% especially 1 to 3% by weight. Aqueous solutions up to 80% by weight concentration are obtainable, but these normally require some dilution to provide compositions suitable to be administered to humans or animals. Our invention includes concentrates for dilution to provide pharmaceutical, veterinary or cosmetic preparations. THP salts are generally non-carcinogenic and non-mutagenic, but exhibit toxic effects especially on liver cells. Their toxicity in topical applications is generally low, but care must be taken in administering them internally.

The invention is of particular value for the treatment of vertebrates including: mammals such as cats, dogs and other carnivores, horses, sheep, pigs, cattle, goats, camels, deer and other ungulates, mice, hamsters, gerbils and other rodents, man and other primates; birds such as chickens, geese, ducks, turkeys and cage birds; reptiles; and fish.

The invention will be illustrated by the following examples.

Example 1

In the following Tables 2 to 21 the material D denotes a 75% by weight aqueous solution of tetrakis(hydroxymethyl) phosphonium sulphate and Kathon WT is a registered Trade Mark and represents a widely used proprietory biocide which is an aqueous solution of a mixture of 2-methyl-4-isothiazolin-3-one and 5-chloro-2-methyl-4-isothiazolin-3-one. The results show that material D has a high degree of lethal activity to bacteria within 2 to 6 hours of exposure at concentrations of at least 20 ppm and a high degree of lethal activity to the fungi at 100-150 ppm after 24 hours.

1. **Microbial strains**

TABLE 1

(a) Bacteria

The following bacterial strains were used in the tests:

Streptococcus pyogenes NCTC 8198
Streptococcus faecalis ATCC 19433
Sarcina lutea ATCC 9341
Proteus mirabilis NCTC 8559
Proteus vulgaris NCTB 4175
Klebsiella pneumoniae NCTC 10341
Salmonella typhimurium NCTB 10258
Salmonella enteritidis NCTC 6676
Shigella boydii NCTC 9328
Bacillus subtilus ATCC 6633
Bacillus cereus ATCC 11778

(b) Yeasts and fungi

The following yeast and fungal strains were used in the tests:

Candida albicans ATCC 10231
Candida tropicalis NCPF 3111
Absidia corymbifera NCPF 2001
Sporotrichum schenkii NCPF 3182
Trichophyton rubrum NCPF 197
Trichophyton mentagrophytes NCPF 351
Microsporum Canis NCPF 351
Penicillium funicolosum CMI 114933
Aureobasidium pullulans CMI 45533

2. **Preparation of inocula**

Inocula for the bacterial strains were prepared from cultures on Tryptone soy agar (TSA, Oxoid CM 131) incubated at 37°C for 24 hours. Surface growth of the organisms was suspended in sterile physiological saline and diluted with this medium to give 50% transmission at 520 nm on an SP 600 spectrophotometer, an approximate yield of 10^8 colony forming units (cfu) per ml. For use as inocula these suspensions were further diluted in sterile physiological saline to give an expected final concentration in the test solutions of 10^4 to 10^5 of cfu/ml.

Inocula for the two yeast (Candida) strains wre prepared from cultures on Sabouraud dextrose agar (SDA Oxide CM 141) incubated at 37°C for 48 hours. Surface growth of the organisms was suspended in sterile physiological saline and standardised by plate counts to contain approximatedly 10^6 cfu/ml.

For use as inocula these suspensions were diluted to give an expected final concentration in the test solutions of 10^4 to 10^5 cfu/ml.

Inocula for the fungal strains were prepared by sub-culturing the organisms from SDA into Sabouraud liquid medium (SLM, Oxoid 147) and incubating at 30°C for 5 to 10 days. Mycelial growth was then broken down by shaking the cultures with glass beads and the resulting suspensions were standardised by plated counts to contain approximately 10^6 cfu/ml.

3. **Test media and inactivators**

All tests were carried out in phosphate buffered saline (PBS) prepared from Oxoid tablets (Dulbecco A, Oxoid BR14a) and having the formula:

Sodium chloride 8 g/litre
Potassium chloride 0.2 g/litre
Disodium hydrogen phosphate 115 g/litre
Potassium dihydrogen phosphate 0.2 g/litre
pH 7.3 g/litre

Samples from the inoculated test and control preparations were diluted 1 ml to 9 ml in 0.1% peptons water containing 1% v/v Tween 80 as an inactivator, and serially diluted in further ten-fold steps in the same dilutent.

The media used for preparing plate counts from the diluted samples were:

(a) for bacterial strains - Tryptone soy agar containing 0.2% sodium thioglycollate
(b) for yeast and fungal strains - Sabouraud dextrose agar containing 0.2% sodium thioglycollate.

4. **Test solutions of D or Kathon WT**

For preparation of the test series each was diluted in PBS 1 part in 1000 parts to give a stock solution of 1000 ppm. This was freshly prepared on each test day.

The stock dilution was then further diluted to give the test series of:

(b) 500, 200, 100, 50 and 20 ppm for the organisms tested Strep. pyogenes, Strep. faecalis, Shigella boydii, Salmonella enteritidis and Klebsiella pneumoniae) and:
(c) 500, 100, 20, 5 and 1 ppm for the remainder of the test organisms.

5. **Test procedure**

The test solutions as described in (5) above were prepared in 50 ml volumes and the test solutions plus a 100 ml volume of PBS (as control) were inoculated with appropriate volumes (0.5 to 1 ml) of the inocula prepared as described in (2) above, shaken to evenly distribute the inoculum and held at room temperature. Immediatedly after inoculation (time 0) and then at pre-determined times 0.1 ml aliquots were removed from the test and control solutions for counting.

The 0.1 ml samples were serially diluted in hundred-fold steps in the peptons water/Tween 80 diluent and 1 ml volumes of the dilutions were used to prepare duplicate pour-plates in TSA/sodium thioglycollate medium for the bacteria and Sabouraud/sodium thioglycollate medium for the yeasts and fungi.

The bacterial count plates were incubated at 37°C for 24 hours, the yeast (Candida) count plates at 37°C for 48 hours and the fungal count plates at 30°C for 5 to 10 days.

Developing colonies were then counted and by reference to the appropriate dilution ratios the numbers of surviving organisms at each compound concentration/time point were calculated.

TABLE 2

Recovery of viable cells of Streptococcus pyogenes NCTC 8198 following exposure to D and Kathon WT in phosphate buffered saline

Compound / Conc. in ppm	Recovered viable cells cfu/ml — Sampling time after inoculation			
	0	2 hr	6 hr	24 hr
Material D				
500 ppm	1.8×10^5	0	0	0
200 ppm	1.2×10^5	0	0	0
100 ppm	1.4×10^5	0	0	0
50 ppm	1.4×10^5	0	0	0
20 ppm	2.0×10^5	1.7×10^2	0	0
Kathon WT				
500 ppm	2.8×10^5	4.4×10^5	3.0×10^5	1.1×10^5
200 ppm	8.0×10^4	2.1×10^5	2.8×10^5	1.2×10^5
100 ppm	1.4×10^5	3.6×10^5	1.9×10^5	3.0×10^5
50 ppm	2.1×10^5	7.2×10^5	2.3×10^5	2.2×10^5
20 ppm	1.4×10^5	6.0×10^5	2.2×10^5	6.0×10^5
Control (phosphate buffered saline)	8.7×10^5	3.4×10^5	1.8×10^5	3.7×10^5

TABLE 3

Recovery of viable cells of Streptococcus faecalis ATCC 19433 following exposure to D and Kathon WT in phosphate buffered saline

Compound / Conc. in ppm	Recovered viable cells cfu/ml			
	Sampling time after inoculation			
	0	2 hr	6 hr	24 hr
Material D				
500 ppm	1.3×10^5	0	0	0
200 ppm	3.2×10^5	0	0	0
100 ppm	2.8×10^5	0	0	0
50 ppm	3.0×10^5	0	0	0
20 ppm	4.1×10^5	20	0	0
Kathon WT				
500 ppm	2.6×10^5	1.5×10^5	1.2×10^5	1.4×10^5
200 ppm	6.5×10^5	1.6×10^5	1.9×10^5	1.2×10^5
100 ppm	5.8×10^5	1.4×10^5	1.2×10^5	5.0×10^4
50 ppm	3.3×10^5	1.9×10^5	1.9×10^5	1.8×10^4
20 ppm	3.8×10^5	2.6×10^5	1.1×10^5	2.7×10^4
Control (phosphate buffered saline)	3.8×10^5	2.0×10^5	1.6×10^5	3.1×10^4

TABLE 4

Recovery of viable cells of Sarcina lutea ATC 9341 following exposure to D and Kathon WT in phosphate buffered saline

Compound	Recovered viable cells cfu/ml			
Conc. in ppm	Sampling time after inoculation			
	0	2 hr	6 hr	24 hr
Material D				
500 ppm	1.4×10^4	0	0	0
200 ppm	1.7×10^4	0	0	0
100 ppm	1.5×10^4	1.6×10^4	5.5×10^3	60
50 ppm	1.6×10^4	1.2×10^4	1.8×10^4	6.9×10^5
20 ppm	1.4×10^4	1.6×10^4	1.8×10^4	5.6×10^5
Kathon WT				
500 ppm	1.4×10^4	1.3×10^4	1.4×10^4	1.7×10^4
200 ppm	1.6×10^4	1.5×10^4	1.5×10^4	2.0×10^4
100 ppm	1.7×10^4	1.8×10^4	1.8×10^4	1.8×10^4
50 ppm	1.8×10^4	1.6×10^4	1.6×10^4	1.8×10^4
20 ppm	1.5×10^4	1.6×10^4	5.0×10^4	2.2×10^4
Control (phosphate buffered saline)	1.4×10^4	2.0×10^4	1.6×10^4	1.4×10^6

TABLE 5

Recovery of viable cells of Proteus mirabilis NCTC 8559 following exposure to D and Kathon WT in phosphate buffered saline

Compound / Conc. in ppm	Recovered viable cells cfu/ml			
	Sampling time after inoculation			
	0	2 hr	6 hr	24 hr
Material D				
500 ppm	1.0×10^5	0	0	0
100 ppm	9.5×10^5	0	0	0
20 ppm	1.0×10^6	0	0	0
5 ppm	1.3×10^6	1.2×10^6	1.5×10^6	4.1×10^6
1 ppm	1.6×10^6	1.2×10^6	2.8×10^6	9.0×10^6
Kathon WT				
500 ppm	1.0×10^6	1.7×10^5	4.0×10^2	0
100 ppm	1.2×10^6	1.3×10^5	1.9×10^3	0
20 ppm	1.1×10^6	5.3×10^5	2.5×10^5	5.0×10^2
5 ppm	1.2×10^6	6.5×10^5	2.0×10^5	1.7×10^2
1 ppm	1.2×10^6	9.7×10^5	2.9×10^5	1.7×10^2
Control (phosphate buffered saline)	1.2×10^6	1.0×10^6	2.3×10^6	9.8×10^6

TABLE 6

Recovery of viable cells of Proteus vulgaris NCIB 4175 following exposure to D and Kathon WT in phosphate buffered saline

Compound / Conc. in ppm	Recovered viable cells cfu/ml			
	Sampling time after inoculation			
	0	2 hr	6 hr	24 hr
Material D				
500 ppm	4.0×10^4	0	0	0
100 ppm	1.1×10^6	0	0	0
20 ppm	1.1×10^6	0	0	0
5 ppm	1.0×10^6	9.2×10^6	1.6×10^6	4.1×10^2
1 ppm	1.2×10^6	1.1×10^6	1.6×10^6	2.6×10^6
Kathon WT				
500 ppm	9.5×10^5	2.2×10^5	5	0
100 ppm	8.6×10^5	3.0×10^5	7.0×10^2	0
20 ppm	8.7×10^5	2.2×10^5	1.2×10^4	0
5 ppm	1.1×10^6	3.5×10^5	9.1×10^3	0
1 ppm	9.1×10^5	8.0×10^5	4.9×10^5	6.0×10^2
Control (phosphate buffered saline)	1.2×10^6	1.3×10^6	1.8×10^6	2.3×10^6

TABLE 7

Recovery of viable cells of Klebsiella pneumoniae NCTC 10341 following exposure to D and Kathon WT in phosphate buffered saline

Compound / Conc. in ppm	Recovered viable cells cfu/ml			
	Sampling time after inoculation			
	0	2 hr	6 hr	24 hr
Material D				
500 ppm	6.8×10^5	0	0	0
200 ppm	6.7×10^5	0	0	0
100 ppm	7.9×10^5	0	0	0
50 ppm	8.9×10^5	0	0	0
20 ppm	7.0×10^5	9	0	0
Kathon WT				
500 ppm	8.4×10^5	8.2×10^5	1.5×10^4	0
200 ppm	7.6×10^5	5.2×10^5	9.1×10^4	1.6×10^5
100 ppm	8.3×10^5	6.1×10^5	2.8×10^5	3.9×10^5
50 ppm	1.1×10^6	4.5×10^5	4.7×10^5	3.5×10^4
20 ppm	1.0×10^6	4.6×10^5	8.4×10^5	3.1×10^4
Control (phosphate buffered saline)	9.2×10^5	7.8×10^5	9.5×10^5	2.2×10^6

TABLE 8

Recovery of viable cells of Salmonella typhimurium NCIB 10258 following exposure to D and Kathon WT in phosphate buffered saline

Compound	Recovered viable cells cfu/ml			
Conc. in ppm	Sampling time after inoculation			
	0	2 hr	6 hr	24 hr
Material D				
500 ppm	9.0×10^4	0	0	0
100 ppm	1.1×10^6	0	0	0
20 ppm	1.0×10^6	0	0	0
5 ppm	1.1×10^6	1.5×10^6	1.6×10^6	6.2×10^6
1 ppm	1.0×10^6	1.3×10^6	1.6×10^6	8.1×10^6
Kathon WT				
500 ppm	1.0×10^6	2.1×10^5	1.0×10^4	0
100 ppm	1.3×10^6	9.7×10^5	1.1×10^6	3.6×10^4
20 ppm	1.1×10^6	9.2×10^5	1.1×10^6	2.8×10^5
5 ppm	1.2×10^6	1.1×10^6	1.2×10^6	4.3×10^5
1 ppm	1.2×10^6	1.1×10^6	1.2×10^6	3.2×10^5
Control (phosphate buffered saline)	1.3×10^6	1.4×10^6	1.3×10^6	8.0×10^6

TABLE 9

Recovery of viable cells of Salmonella enteritidis NCTC 6676 following exposure to D and Kathon WT in phosphate buffered saline

Compound Conc. in ppm.	Recovered viable cells cfu/ml Sampling time after inoculation			
	0	2 hr	6 hr	24 hr
Material D				
500 ppm	3.4×10^5	0	0	0
200 ppm	5.9×10^5	0	0	0
100 ppm	7.7×10^5	0	0	0
50 ppm	7.8×10^5	0	0	0
20 ppm	8.5×10^5	16	0	0
Kathon WT				
500 ppm	6.1×10^5	3.1×10^5	2.1×10^5	0
200 ppm	8.2×10^5	5.1×10^5	5.9×10^5	1.6×10^3
100 ppm	5.0×10^5	6.0×10^5	6.0×10^5	1.5×10^4
50 ppm	6.8×10^5	6.9×10^5	1.5×10^5	1.0×10^4
20 ppm	7.6×10^5	6.1×10^5	3.1×10^5	3.3×10^5
Control (phosphate buffered saline)	7.9×10^5	7.5×10^5	1.0×10^6	3.3×10^6

TABLE 10

Recovery of viable cells of Shigella boydii NCTC 9328 following exposure to D and Kathon WT in phosphate buffered saline

Compound	Recovered viable cells cfu/ml			
Conc. in ppm	Sampling time after inoculation			
	0	2 hr	6 hr	24 hr
Material D				
500 ppm	3.1×10^5	0	0	0
200 ppm	3.9×10^5	0	0	0
100 ppm	7.1×10^5	0	0	0
50 ppm	6.6×10^5	0	0	0
20 ppm	6.9×10^5	1.6×10^2	0	0
Kathon WT				
500 ppm	5.2×10^5	1.6×10^5	6.0×10^5	1.5×10^4
200 ppm	6.4×10^5	4.5×10^5	3.8×10^5	2.6×10^3
100 ppm	6.8×10^5	6.2×10^5	4.4×10^5	1.8×10^5
50 ppm	5.1×10^5	5.5×10^5	4.9×10^5	4.8×10^5
20 ppm	5.9×10^5	6.8×10^5	6.3×10^5	7.4×10^5
Control (phosphate buffered saline)	6.9×10^5	9.8×10^5	1.3×10^6	3.0×10^6

TABLE II

Recovery of viable cells of Bacillus Subtilis ATCC 6633 following exposure to D and Kathon WT in phosphate buffered saline

Compound / Conc. in ppm	Recovered viable cells cfu/ml			
	Sampling time after inoculation			
	0	2 hr	6 hr	24 hr
Material D				
500 ppm	1.0×10^3	4.0×10^2	4.0×10^2	36
100 ppm	1.2×10^4	9.0×10^2	7.0×10^2	2.5×10^2
20 ppm	1.0×10^4	9.0×10^2	9.0×10^2	1.0×10^3
5 ppm	1.0×10^4	7.0×10^4	4.9×10^3	1.1×10^3
1 ppm	1.4×10^5	1.3×10^5	6.0×10^4	1.5×10^5
Kathon WT				
500 ppm	6.0×10^4	1.0×10^5	2.0×10^4	1.9×10^3
100 ppm	1.3×10^5	8.0×10^4	1.9×10^4	1.2×10^3
20 ppm	1.1×10^5	9.0×10^4	2.0×10^4	2.4×10^3
5 ppm	1.3×10^5	1.3×10^5	8.0×10^4	6.1×10^3
1 ppm	1.3×10^5	1.0×10^5	1.3×10^5	9.9×10^3
Control (phosphate buffered saline)	1.6×10^4	9.8×10^4	1.6×10^5	2.0×10^5

TABLE 12

Recovery of viable cells of Bacillus cereus ATCC 11778 following exposure to D and Kathon WT in phosphate buffered saline

Compound / Conc. in ppm	Recovered viable cells cfu/ml			
	Sampling time after inoculation			
	0	2 hr	6 hr	24 hr
Material D				
500 ppm	1.4×10^2	10	6	1
100 ppm	1.1×10^5	18	11	4
20 ppm	3.3×10^5	33	12	12
5 ppm	2.4×10^5	5×10^4	1.5×10^2	12
1 ppm	2.7×10^5	1.8×10^5	1.4×10^5	9
Kathon WT				
500 ppm	2.1×10^5	8.0×10^4	2.2×10^5	10
100 ppm	2.3×10^5	1.1×10^4	1.1×10^3	16
20 ppm	1.9×10^5	4.0×10^3	6.0×10^2	21
5 ppm	2.3×10^5	5.0×10^4	5.0×10^2	51
1 ppm	2.1×10^5	1.2×10^5	1.9×10^3	48
Control (phosphate buffered saline)	2.2×10^5	2.1×10^5	1.6×10^5	1.5×10^5

TABLE 13

Recovery of viable cells of Candida albicans ATCC 10231 following exposure to D in phosphate buffered saline

Compound Conc. in ppm	Recovered viable cells cfu/ml Sampling time after inoculation			
	0	2 hr	6 hr	24 hr
Material D				
500 ppm	1.1×10^5	3.3×10^4	2.1×10^3	18
100 ppm	9.5×10^4	7.5×10^4	7.5×10^3	1.2×10^3
20 ppm	9.0×10^4	6.0×10^4	3.0×10^3	1.0×10^4
5 ppm	6.0×10^4	6.1×10^4	2.0×10^4	4.0×10^4
1 ppm	6.0×10^4	8.0×10^4	2.1×10^4	9.8×10^4
Control (phosphate buffered saline)	5.5×10^4	4.0×10^4	7.0×10^4	6.0×10^4

TABLE 14

Recovery of viable cells of Candida tropicalis NCPF 3111 following exposure to D in phosphate buffered saline

Compound / Conc. in ppm	Recovered viable cells cfu/ml			
	Sampling time after inoculation			
	0	2 hr	6 hr	24 hr
Material D				
500 ppm	9.0×10^4	6.0×10^4	2.0×10^4	0
100 ppm	5.9×10^4	5.0×10^4	5.0×10^4	9.1×10^2
20 ppm	5.0×10^4	4.0×10^4	3.5×10^3	1.3×10^4
5 ppm	1.4×10^5	4.3×10^4	4.1×10^4	1.0×10^4
1 ppm	3.1×10^4	6.0×10^4	5.0×10^4	4.4×10^4
Control (phosphate buffered saline)	5.0×10^4	5.0×10^4	6.5×10^4	7.0×10^4

TABLE 15

Recovery of viable cells of Absidia corymbifera NCPF 2001 following exposure to D in phosphate buffered saline

Compound / Conc. in ppm	Recovered viable cells cfu/ml			
	Sampling time after inoculation			
	0	2 hr	6 hr	24 hr
Material D				
500 ppm	1.9×10^4	1.0×10^4	2.0×10^3	0
100 ppm	1.6×10^4	1.5×10^4	3.0×10^3	2.0×10^3
20 ppm	1.7×10^4	1.5×10^4	1.6×10^4	1.4×10^4
5 ppm	1.3×10^4	1.8×10^4	1.7×10^4	1.4×10^4
1 ppm	1.5×10^4	1.6×10^4	1.7×10^4	6.0×10^3
Control (phosphate buffered saline)	1.8×10^4	1.4×10^4	1.7×10^4	1.6×10^4

TABLE 16

Recovery of viable cells of Sporotrichum schenkii NCPF 3182 following exposure to D in phosphate buffered saline

Compound	Recovered viable cells cfu/ml			
Conc. in ppm	Sampling time after inoculation			
	0	2 hr	6 hr	24 hr
Material D				
500 ppm	4.0×10^4	9.6×10^3	1.8×10^2	0
100 ppm	3.1×10^4	1.7×10^4	1.0×10^4	6.1×10^3
20 ppm	2.6×10^4	3.0×10^4	3.4×10^4	2.2×10^4
5 ppm	2.7×10^4	3.5×10^4	4.0×10^4	4.0×10^4
1 ppm	3.4×10^4	2.7×10^4	3.6×10^4	4.1×10^4
Control (phosphate buffered saline)	2.9×10^4	3.3×10^4	3.0×10^4	6.0×10^4

TABLE 17

Recovery of viable cells of Trichophyton rubrum NCPF 197 following exposure to D in phosphate buffered saline

Compound / Conc. in ppm	Recovered viable cells cfu/ml			
	Sampling time after inoculation			
	0	2 hr	6 hr	24 hr
Material D				
500 ppm	2.0×10^3	0	0	0
100 ppm	3.0×10^3	3.0×10^3	10	0
20 ppm	4.0×10^3	2.0×10^3	9.0×10^2	3.4×10^2
5 ppm	3.0×10^3	3.0×10^3	3.0×10^2	2.0×10^3
1 ppm	2.0×10^3	2.5×10^3	5.0×10^3	3.0×10^3
Control (phosphate buffered saline)	6.0×10^3	4.0×10^3	3.0×10^3	9.0×10^4

TABLE 18

Recovery of viable cells of Trichophyton mentagrophytes NCPF 410 following exposure to D in phosphate buffered saline

Compound / Conc. in ppm	Recovered viable cells cfu/ml			
	Sampling time after inoculation			
	0	2 hr	6 hr	24 hr
Material D				
500 ppm	1.6×10^4	0	0	0
100 ppm	2.1×10^4	1.2×10^4	1.7×10^2	0
20 ppm	1.7×10^4	2.1×10^4	1.4×10^4	4.0×10^2
5 ppm	1.5×10^4	2.6×10^4	1.9×10^4	3.0×10^3
1 ppm	1.8×10^4	1.9×10^4	2.6×10^4	6.0×10^3
Control (phosphate buffered saline)	1.8×10^4	2.0×10^4	1.9×10^4	4.5×10^5

TABLE 19

Recovery of viable cells of Microsporum canis NCPF 351 following exposure to D in phosphate buffered saline

Compound / Conc. in ppm	Recovered viable cells cfu/ml			
	Sampling time after inoculation			
	0	2 hr	6 hr	24 hr
Material D				
500 ppm	1.3×10^4	3.8×10^2	10	0
100 ppm	1.5×10^4	8.0×10^3	3.0×10^3	30
20 ppm	1.2×10^4	1.4×10^4	6.0×10^3	4.2×10^2
5 ppm	1.3×10^4	8.0×10^3	6.0×10^3	7.0×10^3
1 ppm	1.0×10^4	1.1×10^4	1.1×10^4	1.0×10^4
Control (phosphate buffered saline)	1.0×10^4	1.1×10^4	1.2×10^4	9.0×10^3

TABLE 20

Recovery of viable cells of Penicillium funiculosum CMI 114933 following exposure to D in phosphate buffered saline

Compound	Recovered viable cells cfu/ml			
Conc. in ppm	Sampling time after inoculation			
	0	2 hr	6 hr	24 hr
Material D				
500 ppm	8.0×10^3	6.0×10^3	6.0×10^3	10
100 ppm	8.0×10^3	6.0×10^3	9.0×10^3	8.0×10^3
20 ppm	1.1×10^4	4.0×10^3	8.0×10^3	5.0×10^3
5 ppm	9.0×10^3	7.0×10^3	7.0×10^3	7.0×10^3
1 ppm	1.1×10^4	7.0×10^3	7.0×10^3	6.0×10^3
Control (phosphate buffered saline)	1.4×10^4	1.0×10^4	9.0×10^3	1.0×10^4

TABLE 21

Recovery of viable cells of Aureobasidium pullulans CMI 45533 following exposure to D in phosphate buffered saline

Compound / Conc. in ppm	Recovered viable cells cfu/ml			
	Sampling time after inoculation			
	0	2 hr	6 hr	24 hr
Material D				
500 ppm	4.0×10^3	1.9×10^3	2.0×10^3	2.0×10^3
100 ppm	2.8×10^3	2.1×10^3	3.1×10^3	2.5×10^3
20 ppm	3.0×10^3	3.0×10^3	3.0×10^3	1.9×10^3
5 ppm	3.0×10^3	1.9×10^3	2.1×10^3	3.6×10^3
1 ppm	4.1×10^3	2.0×10^3	2.3×10^3	2.2×10^3
Control (phosphate buffered saline)	3.0×10^3	2.6×10^3	2.6×10^3	3.0×10^4

Example 2

The activity of 50% aqueous bis THP phosphite, 50% aqueous mono THP phosphite and 80% aqueous THP sulphate against Trichophyton rubrum were compared in a 7 day test in phosphate buffered saline solution to determine ED_{50} and ED_{90} values.

Table 22

Concentration ppm (Active Compound)	50% bis THP phosphite Mg. growth dry weight	(% of control)	50% THP phosphite Mg. growth dry weight	(% of control)	80% THP Sulphate Mg. growth dry weight	(% of control)
0	10.6	(100)	7.1	(100)	8	(100)
5	8.7	(82)	9.3	(131)	-	-
8	-	-	-	-	7.3	(92)
15	2.1	(20)	2.8	(39)	-	-
24	-	-	-	-	0	(0)
50	0	(0)	3.1	(44)	-	-
80	-	-	-	-	0	(0)
150	0	(0)	2.3	(32)	-	-
240	-	-	-	-	0	(0)
500	0	(0)	1.6	(23)	-	-
800	-	-	-	-	0	(0)
ED_{50}	10 ppm		11 ppm		14 ppm	
ED_{90}	25 ppm		>500 ppm		20 ppm	

THP chloride, bis THP phosphate, THP borate, THP bromide, THP fluoride, THP acetate, THP citrate, THP lactate and THP tartrate all give substantially similar ED_{50} and ED_{90} results against T. Rubrum to those obtained using bis THP phosphite and THP sulphate.

In contrast under the same conditions phosphorous acid, which is widely used as a fungicide, requires concentrations of the order of 0.1 to 0.2% by weight to produce a useful reduction in the growth of T. Rubrum.

Example 3

THPS was found to give a complete in vitro kill of Naegleria (the protozoon responsible for Amoebic Meningitis) at concentrations of 15 ppm.

Example 4

One of ten Koi Carp, in a fish pond, exhibited symptoms of protozoal infection. 100 ppm of 75% aqueous THP sulphate was dosed to the pond via the oxygenating venturi to provide a concentration of 27 ppm in the pond water. The infected fish recovered fully and none of the other fish became infected. The fish fed normally throughout the treatment and exhibited no signs of distress.

Example 5

A cream for treatment of fungal infections of human skin by topical application comprises:
9% emulsifying wax
15% soft white paraffin
6% liquid paraffin

0.5% citric acid monohydrate
2.5% sodium phosphate
2% THP phosphate
balance sterile water

When the cream is applied twice daily to areas of ringworm infection full remission is normally observed within 1 to 2 weeks.

Example 6

A mouthwash for dilution with an equal volume of warm water prior to use comprises:
1.5gm sodium chloride
1.0gm sodium bicarbonate
2.5ml peppermint emulsion
1ml 75% THP chloride solution
50ml chloroform water
balance to 100ml sterile water

The composition produces rapid alleviation of oral thrush.

Example 7

Nasal drops comprise:
500 mg Ephedrine hydrochloride
500 mg Chlorobutanol
500 mg Sodium Chloride
1ml 75% aqueous THP chloride
balance to 100ml water

Example 8

Foot powder comprises:
25% zinc oxide
25% starch
50% talc

The starch is first mixted with 12%, by weight thereof of 75% aqueous THP sulphate.
The powder produces rapid alleviation of Athletes Foot.

Example 9

A foot spray comprises the starch preparation of example 8 dispersed in a pressure liquified propellent gas, together with a perfume and an antiperspirant. The composition provides reduction in foot odours and is useful in preventing or alleviating Athletes Foot

Claims

1. The therapeutic, prophylactic or cosmetic use for treating the human or animal body of a hydroxyalkylphosphine compound of the formula $(HORPR^1_n)_xX_y$ wherein R is an alkylene group having from 1 to 4 carbon atoms and each R^1 may be the same or different and is an alkyl group having from 1 to 4 carbon atoms or an ROH group, X is an anion such that the compound is at least sparingly soluble in water, n is 2 or 3 and y is 0 or 1 such that (n+y) is 2 or 4; or an at least sparingly water soluble condensate thereof.

2. Use accordingly to claim 1 of a hydroxyalkylphosphine compound of said formula wherein R has 1 carbon atom.

3. Use according to either of claims 1 and 2 of a hydroxyalkylphosphine compound of said formula wherein each R^1 has 1 carbon atom.

4. Use according to any foregoing claim of a hydroxyalkylphosphine compound of said formula wherein R^1 is R(OH).

5. Use according to claim 1 of a water soluble tetrakis (hydroxymethyl) phosphonium salt.

6. A method of treating an infection of human or animal skin which comprises applying thereto a hydroxyalkylphosphine compound as specified in any foregoing claim.

7. A method according to claim 6 for treating fungal or yeast infections.

8. A method according to claim 7 for treating Athletes Foot, Ringworm or Thrush.

9. A method of treating feet to eliminate or reduce malodour which comprises applying thereto a composition comprising a hydroxyalkylphosphine compound as specified in any of claims 1 to 5.

10. A method according to claim 6 of treating cattle suffering from Mastitis which comprises contacting their udders with an aqueous solution of a hydroxyalkylphosphine compound as specified in any of claims 1 to 5.

11. A method of treating human or animal patients suffering from a microbial infection, which method

comprises administering to said patients, orally or parenterally, a composition comprising a hydroxyalkylphosphine compound as specified in any of claims 1 to 5.

12. A method according to claim 11 wherein said microbial infection is a bacterial or protozoal infection.

13. A method according to claim 12 for treating patients suffering from Amoebic Meningitis.

14. A method according to either of claims 6 and 12 of treating patients suffering from a Streptococcal infection.

15. A method according to either of claims 6 and 12 of treating patients suffering from a Proteus infection.

16. A method according to either of claims 6 and 12 treating patients suffering from a Klebsiella infection.

17. A method according to claim 12 of treating patients suffering from a Salmonella infection.

18. A method according to either of claims 1 and 17 which comprises dosing a hydroxyalkylphosphine compound as specified in any of claims 1 to 5 in drinking water supplied to chickens.

19. A method according to claim12 of treating patients suffering from a Shigella infection.

20. A method, according to either of claims 6 and 12, of treating patients suffering from a Bacillus infection.

21. A pharmaceutical, veterinary or cosmetic composition comprising a hydroxyalkylphosphine compound as specified in any of claims 1 to 5, and a pharmaceutically, veterinarily or cosmetically acceptable carrier or diluent.

22. An antiseptic and/or antifungal cream, lotion, paste, collodion or ointment for topical application to the human or animal body comprising a compound as specified in any of claims 1 to 5.

23. An ointment according to claim 22 comprising liquid parafin and/or soft parafin and/or wool fat and/or a wool fat derivative.

24. A cream according to claim 22 comprising the composition according to claim 23 dispersed or emulsified in water.

25. An powder for application to the human or animal body having absorbed therein or adsorbed thereon a hydroxyalkylphosphine compound as specified in any of claims 1 to 5.

26. A composition according to claim 25 comprising talc, zinc oxide, and/or starch or a derivative thereof.

27. A pessary containing a hydroxyalkylphosphine compound as specified in any of claims 1 to 5.

28. An aerosol spray composition comprising a pressure-liquified propellant gas having dispersed therein a composition according to any of claims 21 to 27.

29. A soluble capsule for pharmaceutical or veterinary use containing a hydroxyalkylphosphine compound as specified in any of claims 1 to 5.

30. A tablet for pharmaceutical or veterinary use comprising a hydroxyalkylphosphine compound as specified in any of claims 1 to 5.

31. An aqueous composition for oral or parenteral administration to humans or animals comprising a hydroxyalkylphosphine compound as specified in any of claims 1 to 5.

32. A mouthwash according to claim 31.

33. Nasal drops according to claim 31.

34. A shampoo comprising at least 0.2% by weight of a hydroxyalkylphosphine compound as specified in any of claims 1 to 5.

35. A soap bar containing at least 0.2% by weight of a hydroxyalkylphosphine compound as specified in any of claims 1 to 5.

36. A veterinary dip containing at least 0.2% by weight of a hydroxyalkylphosphine compound as specified in any of claims 1 to 5.

37. A composition according to any of claims 21 to 36 containing from 0.2% to 20% by weight of said hydroxyalkylphosphine compound.

38. A composition according to claim 37 containing from 1 to 10% by weight of said hydroxyalkyl phosphine compound.

39. A composition according to any of claims 21 to 38 additionally comprising at least one other active ingredient selected from fungicides, bactericides, synergists, antiperspirants, styptics, carboxymethyl cellulose, soaps, surfactants, polymeric thickening agents, wetting agents, foam controlloing agents, perfumes, flavouring, colouring, deodorants, reodorants and antiseptics.

40. A concentrate adapted on dilution with water to provide a composition according to any of claims 21 to 39.

41. A use or method according to any of claims 1 to 20 which comprises dosing said hydroxyalkylphosphine compounds to an infected patient at a level adapted to provide a concentration of said compound at the site of infection below that which is toxic to said patient and sufficient to inhibit the development of the infection.

42. A use or method according to claim 41 wherein said concentration is between 1 and 2000 ppm.